台灣癌症醫誌（J. Cancer Res. Pract.）2(4), 308-313, 2015 DOI: 10.6323/JCRP.2015.2.4.5

journal homepage:www.cos.org.tw/web/index.asp

Case Report

Multiple Spinal and Bone Metastases as the Initial Presentation of Small Cell Carcinoma of the Prostate

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Abstract.

Small cell carcinoma (SmCC) of the prostate is a very rare and aggressive type of prostatic cancer. It is hard to early diagnose and most cases are diagnosed at advanced stage. The bones, liver, regional and distant lymph nodes are the most common sites of metastasis. The treatment for SmCC of the prostate is different from that of acinar adenocarcinoma. While chemotherapy is suggested, there is no standard regimen, let alone personalized strategy. Additionally, hormone therapy does not often work for this type of prostate cancer. Here, we report a rare case of SmCC of the prostate who initially presented with lower cervical spine radiculopathy.

Keywords **:** small cell carcinoma, prostate, spinal metastasis

病例報告

以骨及脊椎轉移作為初期表徵的前列腺小細胞癌

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中文摘要

前列腺小細胞癌在臨床上罕見且不易早期診斷，過去統計上的發生率占前列腺癌約1%，其病理特點為細胞較小，分化較低，PSA 可陰性，且多種神經內分泌標記物可陽性，例如: chromogranin A 及 synaptophysin。其臨床症狀常以泌尿道排尿阻塞症狀表現，而實驗室檢查較難有早期協助診斷的工具，臨床上常用的 PSA 可不升高。而因為發病年齡較輕，故易誤診為慢性前列腺炎或前列腺肥大。而治療上早期以手術為主，但因不易早期發現，故病人多只能接受化學治療併放射治療作疾病控制及症狀緩解，亦為治療效果不彰的原因之一，我們在此提出一位前列腺小細胞癌的病例，病人臨床上以背痛及肢體麻表現而無泌尿道相關症狀，在疾病初期亦不易確定診斷，之後接受化放療後，疾病控制約十個月。藉由此個案提供臨床醫師相關治療經驗，並希望在未來能對此族群有更大規模的研究及治療策略以改善治療成效。

關鍵字: 小細胞癌、前列腺、脊椎轉移

INTRODUCTION

Extrapulmonary small cell carcinomas are extremely rare entities and they account for approximately 2.5 to 5% of all small cell carcinomas (SmCC) in the United States [1,2]. Among them, approximately 10% of cases occur in the prostate which was first described by Wenk et al. [3]. The disorder is distinct from the far more common prostatic adenocarcinomas, and it is characterized by earlier onset and more aggressive behavior [4]. The serum levels of the prostate specific antigen (PSA) in SmCC do not correlate with disease activity and are not useful for posttreatment surveillance as in prostate adenocarcinoma [5]. We report on a rare case of SmCC of the prostate who initially presented with lower cervical spine radiculopathy.

CASE REPORT

A 53-year-old man presented to the emergency department with chronic progressive persistent dull backache. He had also experienced numbness without loss of strength in his right upper arm for three weeks. He denied any previous medical or traumatic history. His vital signs were within normal limits on admission. Physical examination disclosed insignificant abnormalities and muscle strength was 5/5 in all four limbs. Sensory deficit in a dermatomal distribution of T1 was observed, and digital rectal exam (DRE) did not show nodules, asymmetry or induration of the prostate.

The plain radiographs of the cervical and thoracolumbar spine showed small osteophyte formation of cervical vertebral bodies and mild degenerative change with marginal spurs formation of the thoracolumbar spine. Electromyography and nerve conduction studies showed insignificant results. Magnetic resonance imaging (MRI) of the cervical spine showed numerous small, similar-appearing hypodense lesions distributed throughout the cervical and thoracic bodies. Tumor impingement upon the right T1/2 foramen was also noted (Figure 1).

Laboratory studies showed an elevated carcinoembryonic antigen (CEA) level (7.26 ng/ml, normal 0.0-5.0 ng/ml), carbohydrate antigen 19-9 level (111.4 unit/ml, normal 1.0-35.0 unit/ml) and a normal PSA level (1.41 ng/ml, normal 0-3 ng/ml). The total white blood cell count was 6,300/μl (normal 4,000-11,000/μl), hemoglobin was 13.2 g/dl (13.5–17.0 g/dl), and platelet count was 201,000/μl (150,000–400,000/μl).

Computed tomography (CT) scan of the abdomen revealed several nodules near the left pararectal and iliac vessel areas, and the largest nodule was 2.4 x 1.3 cm in size in the left pararectal area. Colonoscopy showed a 2 cm mass in the ascending colon, which was pathologically proven to be an adenoma.

Under the impression of malignancy with T-spine involvement, the patient received whole body positron emission tomography (PET)/CT scan and intense ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake over the cervical, thoracic, lumbar spines, sacrum, rib cages, pelvis, right femur, right ascending colon and prostate was seen (Figure 2).

Transrectal ultrasound-guided needle biopsy of prostate showed SmCC Gleason grade 5+5. Immunohistochemical staining was negative for PSA, positive for cytokeratin 18, chromogranin A (CgA), synaptophysin (Syn), and thyroid transcription factor-1 (TTF-1), and focally positive for neuron-specific enolase (NSE) (Figure 3).

Under the diagnosis of poor differentiated neuroendocrine SmCC of the prostate, cT2cN1M1c, stage IV the patient received six cycles of triweekly intravenous etoposide 80 mg/m^2 (on day 1) and cisplatin 80 mg/m^2 (daily on days 1 through 3). Palliative radiotherapy was given with 30 Gy in 10 fractions for bony metastasis. After the sixth cycle, follow-up MRI

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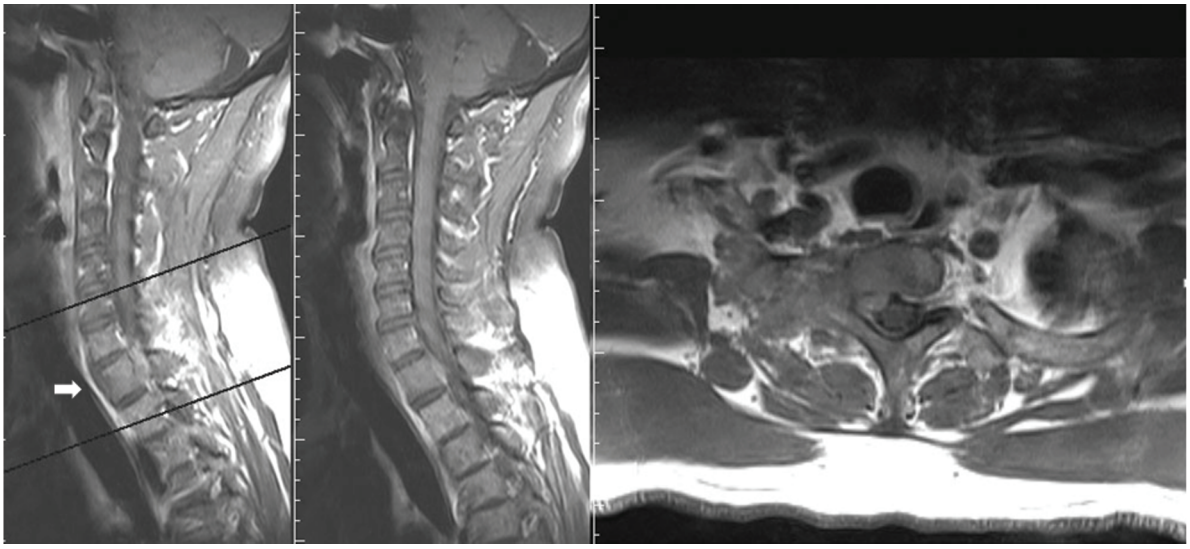

Figure 1. MRI of the cervical spine revealed numerous small, similar-appearing hypodense lesions distributed throughout the cervical and thoracic bodies. Tumor impingement upon the right T1/2 foramen is seen (arrow)

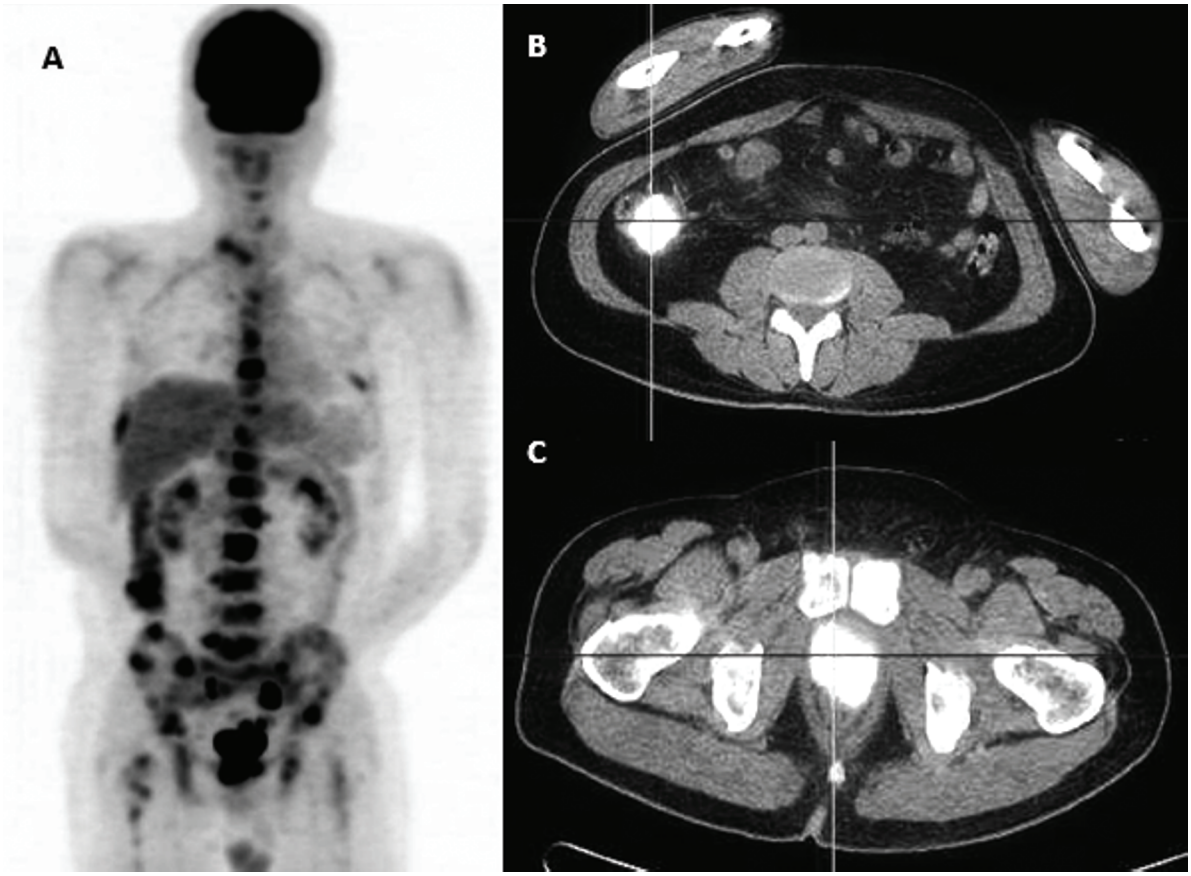

Figure 2. Whole body PET/CT scan showed intense ^{18}F-FDG uptake in the entire skeleton, including cervical, thoracic, lumbar spines, sacrum, rib cages, pelvis, and right femur (A); Unusually high FDG uptake was found in the right abdomen with several focal intense FDG activity localized in the right ascending colon (B) and prostate region (C)

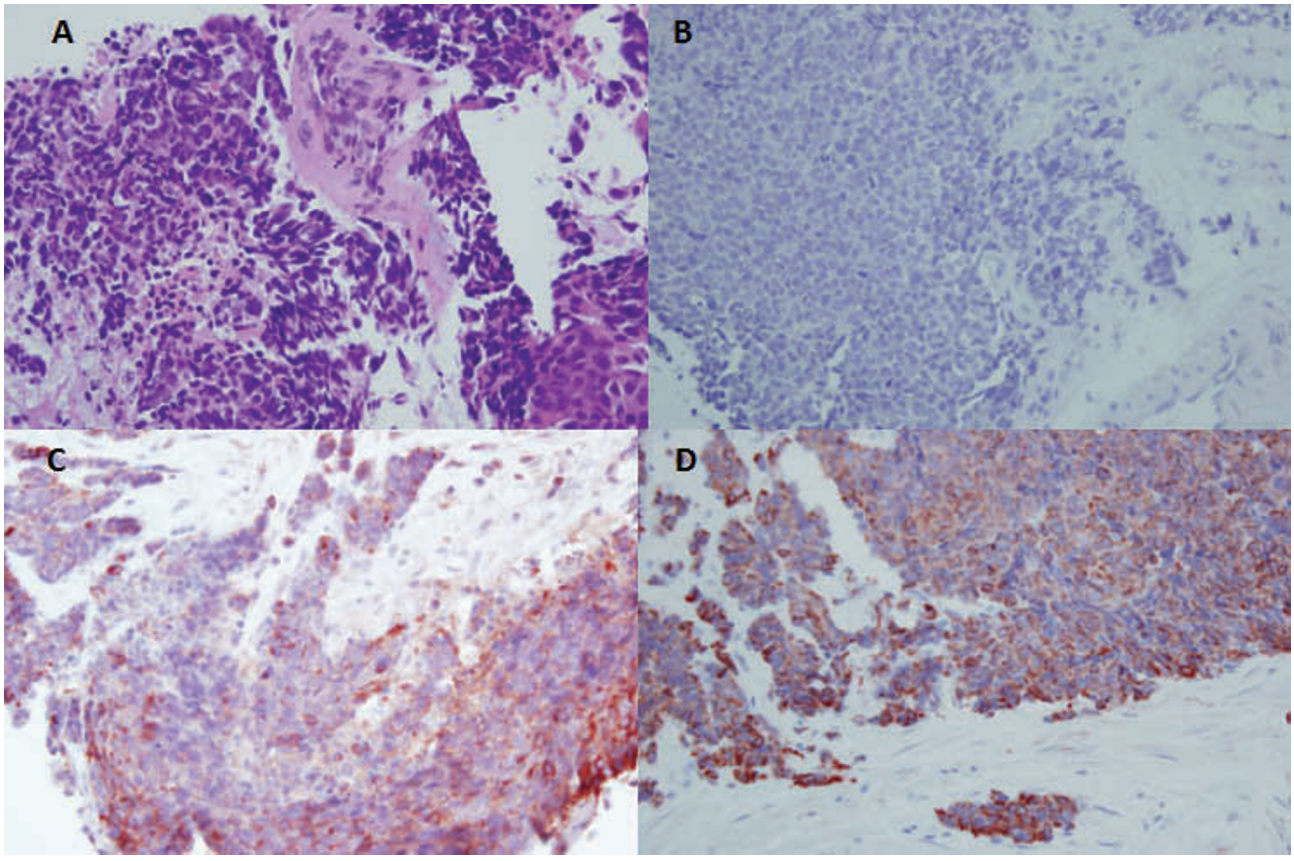

Figure 3. Transrectal ultrasound-guided needle biopsy of prostate showed (A) Tumor cells characterized by hyperchromatic nuclei, a very high N/C ratio, fine granular chromatin and inconspicuous nucleoli infiltrating the stroma. (Hematoxylin-Eosin stain ×200). Immunohistochemical staining was negative for PSA (B), positive for chromogranin A staining (C), and positive for cytokeratin 18 in membrane and dot-like patterns (D)

showed stable disease, but he succumbed to profound septic shock 4 months later, 10 months after the date of his initial diagnosis.

DISCUSSION

Prostate SmCC is a poorly differentiated tumor with a very low incidence, accounting for less than 2% of all prostate cancers [6,7]. SmCC has an aggressive character and easily metastasizes to the liver, bones, bladder, rectum, central nervous system and lungs [8]. Unlike patients with prostate adenocarcinoma, most patients with SmCC of the prostate are symptomatic at diagnosis. Signs and symptoms, in order of frequency, include obstructive, neurologic, and constitutional symptoms, followed by symptoms from paraneoplastic syndromes, bone pain, hydronephrosis, abdominal pain, hematochezia, and hematuria [9].

However, it is sometimes difficult to detect early due to negative DRE and disproportionately low PSA levels in the presence of metastatic disease. A complete physical examination and laboratory studies should be performed due to the risk of paraneoplastic syndromes, including Cushing's syndrome, peripheral neuropathy, membranous nephropathy, and hypercalcemia without bone metastases [10].

SmCC of the prostate usually stains positive for NSE, synaptophysin and chromogranin A, and negative for androgen receptor and PSA [11]. TTF-1 can

be positive in up to half of small cell carcinomas and is not found in the poorly diffrentiated adenocarcinomas [12,13]. TTF-1 is a tissue specific transcription factor expressed in epithelial cells of the thyroid and lung as well as in certain areas of the brain [14]. SmCC of the prostate can be distinguished from metastasis from the lung based on immunohistochemical staining for NSE, synaptophysin, and chromogranin A, ERG rearrangement (positive in 50% of cells) or MYC amplification (positive in 50% of cells) in genetic studies [15-17].

Interestingly, our case presented with backache and limb numbness rather than obstructive urinary symptoms. In addition, constitutional symptoms such as body weight loss or poor appetite were not observed. The negative DRE and normal serum PSA level increased the difficulty of early detection.

To date, no standard chemotherapy regimen has been formally acknowledged for SmCC of the prostate due to the small number of cases [6]. Surgery is recommended for early lesions and chemotherapy is the main strategy in metastatic disease with radiation for local control [5,18,19]. Because most SmCC cases are already in advanced stage when diagnosed, poor prognosis is expected. In practice, chemotherapy regimens for SmCC of the lung are typically used to treat the origin of prostate. It has been reported that the combined use of etoposide/cisplatin (EP) had an efficacy of around 61% in SmCC of the prostate [20]. Recent studies reported that the median survival time ranged from 5 to 17.5 months [5,20-22]. Additionally, SmCC is a hormone-independent tumor, and androgen deprivation therapy is not effective for SmCC [23]. Neuroendocrine diffrentiation may also play an important role in the development of androgen resistance and may limit responsiveness to androgen signalling inhibition [19,24,25]. Our case received the EP regimen and overall survival was 10 months. The initial purposes of radiotherapy are symptom control and palliation. In younger patients, more aggressive radiotherapy strategies may be considered due to radiosensitivity of SmCC of the prostate [26].

In conclusion, SmCC of the prostate is a rare, aggressive disease with poor prognosis and is not associated with elevated serum PSA. Further studies should be undertaken to determine the appropriate treatment protocols for patients with SmCC of the prostate.

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